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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/596,968	WOLOSZCZUK ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29,31-38,47,57 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29,31-38,47,57 and 58* is/are rejected.

7)☒ Claim(s) *47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 July 2009* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/14/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's amendment filed 7/14/2009 is acknowledged and has been entered. Claims 29, 35, 37, and 47 were amended. Claims 29, 31-38, 47, and 57-58 are currently pending and subject to examination below.

Rejections Withdrawn

2. The rejections under § 112, 2nd paragraph not reiterated below have been withdrawn.

Priority

3. Acknowledgment is made of the present application as a proper National Stage (371) entry of PCT Application No. PCT/EP05/54446, filed 9/8/2005, which claims foreign priority under 35 U.S.C. 119(a)-(d) to Application No. A 1505/2004, filed on 9/8/2004 in Austria.

Drawings

4. The drawings are objected to because in the Replacement drawings filed 7/14/2009, some of the letters in Figures 1B and 2B are depicted in italics. However, it is not explained in the drawings or in the specification what is being denoted by the use of italics for some of the amino acid residues.

5. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet,

even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Alternatively, Applicant may address this issue by amending the specification (for example in the Brief Description of the Drawings) so as to indicate what is being denoted by italics. Applicant is reminded that no new matter may be introduced into the disclosure.

Specification

6. The specification is objected to because the heading "The Brief Description of the Drawings" is not present in the specification. A reference to and brief description of the drawing(s) is required as set forth in 37 CFR 1.74. See MPEP § 608.01(f). Applicant is requested to insert this heading on page 11 prior to the discussion of Figures 1-4.

Claim Objections

7. Claim 47 is objected to because of the following informalities: in the last line of the claim "employing it in method of claim 29" should apparently read "employing it in the method of claim 29". Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 29, 31-38, 47, and 57-58 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining that either canine proBNP or fragments thereof that comprise the recited epitope are present in a sample, does not reasonably provide enablement for (1) methods in which the presence of canine proBNP *and* the presence of fragments thereof are separately determined; for (2) methods in which the concentration of canine proBNP *and* the concentration of fragments thereof are determined; or for (3) methods in which the presence or concentration of *any* fragments of canine proBNP are determined. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The nature of the invention relates to an immunoassay method employing at least one antibody that binds to canine proBNP within the region defined by amino acids 20 to 86. It is noted that it is not entirely clear what amino acid sequence is intended (see § 112, 2nd paragraph

issues discussed below). Considering the claims in light of the elected species of amino acids 32 to 48 of canine proBNP, it appears that Applicant intends this epitope to refer to the last sequence depicted in Figure 1B (SEQ ID NO:3).

The specification discloses assays in which such antibodies are contacted with a sample and the amount of antibody binding is assessed via a labeled competing antigen or alternatively via a labeled antibody (see especially pages 9-10).

The prior art recognized that mammalian proBNP (including canine BNP) may be cleaved to produce a carboxy-terminal, 32-amino acid fragment (known variously in the art as mature BNP, α-BNP, or simply BNP), as well as an amino-terminal fragment. The amino-terminal fragment apparently varies in length in different species, but it is known in the art as BNP(1-76) in the case of the human fragment which is 76 amino acids; or alternatively as NT-proBNP. See Asada et al. (EP 1 016 867 B1, of record) at [0002] and [0010]-[0012].

The SEQ ID NO:3 epitope to which Applicant's antibody binds is present within the amino-terminus of proBNP, prior to the cleavage site. See for example Seilhammer et al. U.S. 6,586,396 B1 (of record) at Figure 8.

This means that antibodies that bind to SEQ ID NO:3 would bind to both full-length proBNP as well as to NT-proBNP, as both of these molecules include the SEQ ID NO:3 epitope bound by the antibodies. The antibodies would also necessarily bind to any other fragments of proBNP that comprise this epitope.

The claims recite that the "presence and/or concentration of the canine proBNP and fragments thereof" are determined by the claimed methods. When the claims are given their broadest reasonable interpretation, this language is interpreted to encompass methods in which

antibody binding is used to determine whether proBNP is present in the sample as well as whether fragments thereof are present in the sample. In addition, the claims encompass methods in which the *concentration* of proBNP as well as the *concentration* of fragments thereof are determined by the claimed methods. This language therefore implies that the results obtained by the method would allow one to determine not only whether proBNP is present in the sample, but also whether fragments thereof are also present.

However, because antibodies that bind to SEQ ID NO:3 would bind to both full-length proBNP as well as to any fragments that comprise SEQ ID NO:3 (such as NT-proBNP), an immunoassay employing an antibody directed to SEQ ID NO:3 would produce a signal in the presence of either proBNP or fragments thereof that comprise SEQ ID NO:3, such as NT-proBNP.

The specification fails to provide direction or guidance with regard to distinguishing proBNP from its fragments. It is not apparent how the claimed methods could be used to separately determine the presence of proBNP and its fragments by antibody binding, as both proBNP and fragments thereof that comprise the antibody epitope would all be immunoreactive in the assay. Although a positive assay result would indicate that molecules presenting the SEQ ID NO:3 epitope are present in the sample, the assay does not distinguish between proBNP and fragments thereof that comprise SEQ ID NO:3. Consequently, additional studies would clearly be necessary to determine the identities of the sample components. Therefore, simply performing the disclosed methods would not allow one to determine whether the sample has proBNP, fragment(s) thereof, or alternatively a mixture of proBNP and fragment(s).

Similarly, the specification also fails to provide direction or guidance with regard to how to *quantify* proBNP and its fragments according to the claimed methods. Because any fragments comprising SEQ ID NO:3 present in the sample would also bind to the antibody in addition to proBNP, the resulting assay signal could not be directly used to quantify proBNP. Similarly, the assay signal could not be directly used to quantify proBNP fragments.

With respect to (3), the claims encompass determining the presence and/or concentration of *any* fragment of proBNP. However, as discussed above the epitope bound by the antibody is present within the amino-terminal portion of proBNP and not within the carboxy-terminal portion that corresponds to mature BNP. Consequently, the antibody used for the assay would not bind to BNP or to other fragments that lack the SEQ ID NO:3 epitope.

Furthermore, Applicant has argued on the record for the existence of unpredictable factors, stating that it was not previously known which fragments of canine proBNP circulated in blood or whether the amount of such fragments was sufficient to be detected by immunoassay (Reply of 7/14/2009, page 12, last paragraph). When taken together with such statements, the specification fails to predictably enable one of ordinary skill in the art to use the claimed methods to determine fragments of proBNP that do not contain the SEQ ID NO:3 epitope.

In summary, fragments of proBNP that comprise the recited epitope were known in the prior art; such fragments would cross-react with the antibody used for the claimed immunoassay method. Absent direct or guidance with regard to how to distinguish proBNP from such fragments by the disclosed immunoassay methods, the specification fails to teach the skilled artisan how to carry out the claimed invention in its full scope, as simply assessing the amount of

antibody binding would not be sufficient to distinguish proBNP from its fragments or to separately determine the concentrations of proBNP or its fragments.

The Examiner's use of terminology above in describing elements of the disclosed invention should not be taken to mean that such terminology, if incorporated into the claims, would comply with the provisions of § 112, 1st paragraph; support for any amendments to the claims must have basis in the original disclosure.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 29, 32-38, 47, and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claims 29 and recite "amino acids 20 to 86 of canine proBNP". The specification apparently discloses partial sequence information for the canine proBNP in Figure 1B, which lists for example the amino acid sequence corresponding to amino acids 32 to 48 of canine proBNP as Epitope 3 (SEQ ID NO:3).

However, the full amino acid sequence of canine proBNP is not disclosed in the specification. In addition, the sequence corresponding to "amino acids 20 to 86 of canine proBNP" is neither depicted in the Figures nor disclosed elsewhere in the specification. Therefore, there is not enough information in the specification to uniquely identify "amino acids 20 to 86 of canine proBNP".

The specification indicates that the amino acid sequence for canine BNP has been published in the Swiss-Prot database under the accession No. P16859 (see page 4).

However, discrepancies were noted upon comparison of the partial sequence information listed in Figure 1B of the specification with the sequence published as Swiss-Prot accession No. P16859 (see the information as retrieved from the UniProtKP/Swiss-Prot database, http://www.uniprot.org/uniprot/P16859, on 3/10/2009).

For example, the amino acids numbered as "amino acids 32 to 48" of canine proBNP in Figure 1B of the specification do not correspond to amino acids 32 to 48 of accession No. P16859 (see the attached information for P16859 at the top of page 3). It appears that Applicant is employing a different numbering scheme. This raises ambiguity as to what specific amino acid sequences are intended. Consequently, the reference in the claims to particular amino acid sequences of canine proBNP by amino acid numbers alone is insufficient to uniquely identify the intended sequences.

In addition, other researchers have reported sequence information for canine proBNP that differs from the P16859 sequence. In particular, Seilhamer et al. (U.S. 6,586,396 B1, of record) depicts a dog preproBNP sequence in Figure 8 that is not the same as the P16859 sequence (see the third row of Figure 8 where the sequence departs for several residues).

In summary, the specification does not provide enough information to adequately identify the recited amino acid sequences. Although reference is made to amino acid sequence information in a public database, the database sequence conflicts with the partial amino acid sequence information disclosed in the present application. In addition, the specification has not effectively incorporated by reference to the database amino acid sequence information.

Furthermore, it appears that differing amino acid sequence information was reported for canine proBNP. For these reasons, the metes and bounds of the claim are unclear.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 29, 31-33, 37-38, 47, and 57-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacDonald et al. ("Brain natriuretic peptide concentration in dogs with heart disease and congestive heart failure" J Vet Intern Med. 2003 Mar-Apr;17(2):172-7) in view of Asada et al. (EP 1 016 867 B1, of record) and in light of the evidence of Harlow & Lane ("Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1988, pages 23-24, and 76), the Academic Press Dictionary of Science and Technology (definition for the term "polyclonal"; Oxford: Elsevier Science & Technology (1996); retrieved October 22, 2008, from http://www.credoreference.com/entry/3144515/), Janeway et al. (Immunobiology: the Immune System in Health and Disease (1999), Elsevier Science Ltd/Garland Publishing, New York, NY, Fourth Edition, pages 34-35), and Wolfe (Wolfe, S.L., Molecular and Cellular Biology, 1993, pages 790-793).

MacDonald et al. teaches that brain natriuretic peptide (BNP) is a recognized biomarker of cardiac disease and congestive heart failure in humans (the abstract). The authors performed clinical studies on dogs, in order to assess whether BNP is also a biomarker of canine heart

disease. In particular, MacDonald et al. measured canine BNP levels in plasma samples from normal dogs and from dogs with heart disease or heart failure, and observed a significant positive correlation with disease (ibid and pages 174-176, "Discussion"). In addition, BNP levels increased with increasing severity of disease (ibid and pages 173-174, "Results"). MacDonald et al. conclude from these studies that increases in BNP may be used to predict death due to cardiovascular disease in dogs, much like in human medicine (see page 175, last paragraph to page 176, second paragraph).

The teachings of MacDonald et al. indicate that BNP is indicative of disease not only in humans, but also in dogs.

It is noted that MacDonald et al. measured BNP-32 (which is a fragment of proBNP corresponding to the carboxy-terminal 32 amino acids of proBNP which is released upon proteolytic cleavage) by radioimmunoassay (page 173, left column), but do not provide details regarding the measurement.

The teachings of MacDonald et al. differ from the claimed invention in that while the reference determined the concentration of the BNP-32 fragment of canine proBNP by immunoassay, the reference fails to apparently teach the use of an antibody that binds to an epitope within amino acids 20 to 86 of canine proBNP.

Asada et al. teach that BNP-32 (also referred to in the reference as α-BNP or simply BNP) is first synthesized as the preprohormone prepro-BNP [0002]. This preprohormone includes a signal sequence which is cleaved to give pro-BNP (also referred to in the reference as γ-BNP) (ibid and [0010]). In the case of humans, pro-BNP has a total of 108 amino acids [0011]. Pro-BNP is then further split to produce BNP-32 and BNP(1-76). The latter fragment is also

referred to in the reference as γ-BNP(1-76). BNP-32 is the carboxy-terminal fragment of proBNP, while BNP(1-76) is the amino-terminal fragment of proBNP [0007].

Asada et al. teach in blood, BNP exists in the form of proBNP or its degradation product, and not in the form of BNP-32 which was previously considered dominant [0008]. Asada et al. further teach that pro-BNP is more stable than BNP-32 in blood (ibid). Due to these facts, Asada et al. concluded that it is indispensable to assay not only BNP-32 but also pro-BNP in order to accurately diagnose cardiac disease.

To accomplish this, Asada et al. teach an immunoassay using a first antibody which is reactive with BNP-32 and a second antibody which is reactive with mammalian prepro-BNP or pro-BNP derivatives but not with BNP-32 [0009], [0012], [0017]. Note that Asada employ the term "derivatives" to encompass pro-BNP itself [0013].

The immunoassay preferably measures the pro-BNP derivative that corresponds to amino acid Nos. 27-134 of SEQ ID NO:1, in the case of human BNP [0019]. This sequence refers to pro-BNP, i.e. after cleavage of the 26-amino acid N-terminal signal sequence from prepro-BNP.

The second antibody used for the assay is preferably specific for amino acids 27-102 of SEQ ID NO:1 in the case of the human sequence [0019]. This sequence corresponds to BNP(1-76), i.e., pro-BNP after the carboxy-terminal BNP-32 has been removed. As one example, Asada et al. raised an antibody against amino acid Nos. 27-64 of SEQ ID NO:1 (i.e., amino acids 1-38 of human pro-BNP). See Example 1, in particular at page 5, lines 24-32.

Although the Example of Asada et al. involved antibodies against human BNP sequences, the reference clearly contemplates any mammalian proBNP and also specifically mentions canine proBNP (see [0010] and claim 1).

In light of the teachings of Asada et al., it would have been obvious to one of ordinary skill in the art to modify the teachings of MacDonald et al. so as to detect not only canine BNP-32 but also canine pro-BNP. In particular, the teachings of Asada et al. indicate that contrary to what was previously thought, BNP exists predominantly in the blood not as BNP-32 but as proBNP or other fragments thereof. In addition, Asada et al. taught that proBNP is more stable in blood than BNP-32. Consequently, Asada et al. teach the need to employ an assay that detects not only BNP-32 but also pro-BNP in order to accurately assess cardiac disease.

As such, when assessing cardiac disease in dogs based on BNP levels according to the method of MacDonald et al., one of ordinary skill in the art would have been motivated to employ this known variation by performing an immunoassay that detects not only canine BNP-32 but also canine pro-BNP in order to obtain more accurate clinical results in dogs in the same way that Asada et al. taught in the case of humans.

Put another way, because Asada et al. teach that their immunoassay produces more accurate clinical results than assays for BNP alone, it would have been obvious to adapt this immunoassay in order to detect pro-BNP and BNP in any mammalian species; when taken together with the teachings of MacDonald et al. that BNP was also well established to be biomarker of heart failure in dogs, it would have been obvious to adapt the immunoassay format of Asada et al. to detect canine pro-BNP and BNP for the purpose of clinical assessment of heart failure in dogs.

The particular solution taught by Asada et al. for performing such an improved BNP immunoassay employs two antibodies, one specific for the carboxy-terminal fragment of pro-

BNP (BNP-32) and one specific for the amino-terminal fragment of pro-BNP (which is BNP(1-76) in the case of human).

The Examiner notes that both human and canine BNP-32 are peptides of 32 amino acids (Asada et al., [0002]). However, the precursor pro-BNP sequences vary slightly depending on species (Asada et al., [0010]). This is why when Asada et al. refer to particular amino acid sequences or residues, the species is also specified (e.g., "In case of human [pro-BNP], it is pro-BNP of 108 amino acids" [0011]).

Therefore, when Asada et al. teach that the second antibody is preferably specific to BNP(1-76) or amino acids 27-102 of SEQ ID NO:1, one of ordinary skill in the art would readily understand that this numbering is referring to the amino-terminal fragment of *human* prepro-BNP (i.e., amino acids 1-76 of proBNP after removal of the 26-residue signal sequence). However, because Asada et al. clearly contemplates *any* mammalian proBNP and also specifically mentions canine proBNP (see [0010] and claim 1), it would have been obvious when performing assays for dog pro-BNP to employ a second antibody that is specific for the amino-terminal fragment of canine pro-BNP. Furthermore, Asada et al. also indicate that like human proBNP, canine proBNP is also cleaved into amino-terminal and carboxy-terminal fragments, although this occurs at Arg 100 rather than Arg 102 due to slight differences in the sequences between species [0010].

When taken together, therefore, it would have been obvious to adapt the two-antibody assay of Asada et al. for detection of canine pro-BNP and BNP by employing a first canine BNP-32-specific antibody together with a second antibody specific for the amino-terminal fragment of canine proBNP which is released upon cleavage at Arg 102 of canine proBNP. One would be

motivated to use two antibodies specific for both the amino-terminal and carboxy-terminal fragments of proBNP in this manner in order to detect not only BNP-32 but also proBNP and its derivatives, which leads to more accurate clinical results as taught by Asada et al.

As discussed above, it is not entirely clear what amino acid sequence is intended by "amino acids 20 to 86 of canine proBNP". However, the instant specification discloses that antibodies against the epitopes in these regions bind to canine NT-proBNP, which is the amino terminal fragment of proBNP or BNP(1-76) in humans (see the specification at page 13). As best understood, therefore, Applicant intends that the antibody binds to canine proBNP within the region that corresponds to the amino-terminal portion of canine proBNP (and not to the portion corresponding to BNP-32).

Therefore, when the claims are given their broadest reasonable interpretation second antibody suggested by the combination of MacDonald et al. and Asada et al. possesses the requisite specificity as it binds to the amino-terminal fragment of canine proBNP (i.e., the canine counterpart of BNP(1-76) in humans).

In addition, no evidence of criticality for the currently claimed range is apparent. Because the teachings of Asada et al. indicate that the region to which antibodies bind on preproBNP influence what fragments of this molecule may be detected, it would have been obvious to arrive at the claimed invention out of the course of routine optimization.

Similarly, with respect to claims 31, 47, and 57-58, although the references do not specifically teach the recited epitope consisting of amino acids 32 to 48 of canine proBNP, absent evidence of criticality it would have been obvious to arrive at the claimed invention out of the course of routine optimization.

It is also noted that Asada et al. teach that the antibodies may be either monoclonal or polyclonal [0018].

Polyclonal antiserum was well known in the art to comprise a mixture of antibodies of different specificities directed toward multiple antigenic determinants present on a particular antigen. See the Academic Press Dictionary of Science and Technology, which defines a polyclonal antibody as a population of heterogeneous antibodies derived from multiple clones, each of which is specific for one of a number of determinants found on an antigen. See also Janeway et al., which provides evidence that antibodies in serum (i.e., antisera) are polyclonal in nature, containing many different antibody molecules that bind to an antigen in many different ways (see p. 34-35, especially at p. 35, the second full paragraph, and Figure 2.1).

It was also well known in the art at the time of the invention that antibodies do not contact the entire surface of their target antigen but rather bind relatively small regions or "epitopes" within said antigen. See Harlow & Lane at pages 23-24, the section entitled "The region of an antigen that binds to an antibody is called an epitope". Harlow et al. also provide evidence that peptide epitopes recognized by antibodies are generally only six amino acids in length, with some researchers reporting epitopes of even smaller size that can be successfully bound by an antibody (see page 76, the first sentence of the section titled "Size of the Peptide"). Similarly, Wolfe discloses that the size of an epitope bound by an antibody is between 3 to 16 amino acids in length (see particularly the bottom of the left column of page 791).

In light of the evidence of Harlow et al. and Wolfe, it is apparent that the recited amino acid sequences possess multiple epitopes available for antibody binding.

Furthermore, in light of the evidence of the Academic Press Dictionary of Science and Technology and Janeway et al., it is apparent that the polyclonal antibodies of Asada et al. would necessarily constitute a homogeneous population of antibodies that bind to the immunogens in many different ways, i.e. to different epitopes within this peptide.

As such, an especially absent evidence to the contrary, it appears that the polyclonal antibodies specific to the amino-terminal fragment of canine proBNP as suggested by the combination of MacDonald et al. and Asada et al. would necessarily include antibodies capable of binding to proBNP at an epitope within amino acids 20 to 86 or 32 to 48 of canine proBNP, given that these sequences share multiple epitopes in common with the amino-terminal fragment of canine proBNP.

Therefore, it would also have been obvious to arrive at the claimed invention of claims 29, 31-38, 47 and 57 by employing antibodies as above that are polyclonal, as taught by Asada et al. As a result of the nature of such antibodies as well as the relationship of the recite epitopes to the amino-terminal fragment of canine proBNP, it appears that the resulting polyclonal antibodies would necessarily possess the recited binding characteristics.

With respect to claim 32, Wolfe (discussed above) provides evidence that antibody epitopes are 3 to 16 amino acids in length. Therefore, antibodies to canine proBNP according to the method of MacDonald et al. and Asada et al. would necessarily possess the recited characteristics.

With respect to claim 37, in the immunoassay of Asada et al., at least one of the first and second antibodies may be immobilized on a solid support [0021]. Therefore, when performing the method of MacDonald et al. using two pro-BNP-specific antibodies as taught by Asada et al.,

it would have been obvious to employ this solid phase-based assay format suggested by Asada et al.

With respect to claim 38, the immunoassay of MacDonald et al. and Asada et al. involves antibody binding and would therefore be considered an "immune binding assay".

With respect to claim 58, Asada et al. teach that the antibodies may be either monoclonal or polyclonal [0018].

15. Claims 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacDonald et al. in view of Asada et al. and in light of the evidence of Harlow & Lane, the Academic Press Dictionary of Science and Technology, Janeway et al., and Wolfe as applied to claim 29 above, and further in view of Harlow & Lane ("Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1988, pages 319, 321-323, 342-345, 353, 561, 563, 574, and 591-593; hereinafter, "Harlow & Lane 2".

MacDonald et al. and Asada et al. are as discussed in detail above. MacDonald et al. teaches radiolabeling (page 173, left column) but does not provide details. Asada et al. exemplifies directly labeling one of the antibodies used for the two-antibody assay (Example 1), and therefore fails to specifically teach the use of at least one further antibody that binds to the antibody discussed in detail above.

Harlow & Lane **2** teach that an antibody can be directly labeled or alternatively used with a labeled secondary reagent that will specifically recognize the antibody (see entire selection, especially at pages 321, 561 and 563). Such a secondary reagent may be (for example) a labeled anti-immunoglobulin antibody specific for the first antibody (see in particular pages 321-323,

345, 574 and 591-593). Detection labels may be, e.g. iodine, fluorochromes, enzymes such as peroxidase, or biotin (p. 342-344, 353, 561, 578-580, 591-593, and 320-323). The choice of direct versus indirect detection depends on the circumstances of the experiment; however, the use of directly labeled antibodies is less sensitive than indirect methods (page 321). In addition, direct labeling requires a new labeling step for every antibody to be studied. In contrast, indirect methods offer the advantages of widely available labeled reagents, which are commercially available and which can be used to detect a large range of antigens. Finally, with indirect labeling the primary antibody is not modified, so potential loss of activity is avoided. Consequently, for the majority of applications indirect methods are the most useful.

Therefore, it would have been further obvious to add a further secondary antibody specific for the proBNP-specific antibody in labeled form in the method of MacDonald et al. and Asada et al. In particular, it would have been obvious to substitute indirect labeling in this manner for the direct labeling methods exemplified by Asada et al. because Harlow & Lane **2** taught for most applications, indirect methods are the most useful and offer numerous advantages over direct labeling.

With respect to claim 36, both MacDonald et al. and Asada et al. teach the use of radiolabels (MacDonald et al. at page 173, left column; radiolabeled iodine is taught by Asada et al. at page 5). Asada et al. also teaches enzymes, fluorescent substances, particles, etc. Similarly, Harlow & Lane that detection labels may be, e.g. iodine, fluorochromes, enzymes such as peroxidase, etc.

Therefore, when employing indirect labeling to label the secondary antibody as discussed above, it would have been further obvious to employ such known labels for their known purpose.

16. Claims 29, 31-38, 47, and 57-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over MacDonald et al. in view of Karl et al. (U.S. 2007/0059767 A1) and Liu et al. ("Cloning and characterization of feline brain natriuretic peptide" Gene 292 (2002) 183–190).

MacDonald et al. is as discussed in detail above, which differs from the claimed invention in that while the reference determined the concentration of the BNP-32 fragment of canine proBNP by immunoassay, the reference fails to apparently teach the use of an antibody that binds to an epitope within amino acids 20 to 86 of canine proBNP.

Karl et al. discuss how human BNP is expressed as the 108-residue precursor proBNP, which is cleaved into N-terminal proBNP (NT-proBNP; amino acids 1-76 of proBNP) and the BNP (amino acids 77-108 of proBNP, also known in the art as BNP-32). See [0007].

Karl et al. teach that because BNP is not very stable, its use as a diagnostic marker is limited [0006]. As an alternative to BNP, Karl et al. teach determining NT-proBNP in a sample using two antibodies that detect different epitopes of this protein fragment, such that they are capable of simultaneously binding (the abstract; [0001]; [0011]-[0025], [0046]; and the claims). The antibodies specifically bind epitopes within the 76-amino acid NT-proBNP molecule, preferably in the amino acid region from 10 to 66, and particularly preferred in the region 10 to 50 or 10 to 38 [0044]. The antibodies may be either polyclonal or monoclonal [0025], and may be raised using recombinant NT-proBNP as an immunogen [0043].

In the Examples, Karl et al. raised both polyclonal and monoclonal antibodies against recombinant human NT-proBNP and subsequently screened them to determine the most reactive epitopes. Antibodies which were reactive with amino acids 30-38 of proBNP (ELQVEQTSL;

SEQ ID NO:8) were successfully produced in this manner (Example 2, see especially at [0062]; and Example 3, see especially Table 2, monoclonal antibody 13.1.18; and Table 3, polyclonal antibody S-9212).

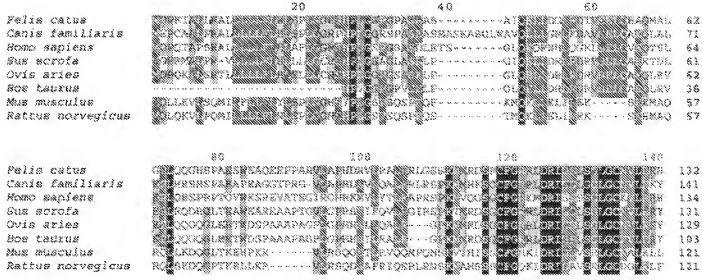
The polyclonal antibody against amino acids 30-38 of human NT-proBNP was used together with a second polyclonal antibody against amino acids 1-21 of this molecule in an immunoassay for determination of NT-proBNP (Examples 4-6). Such assays can be used diagnostically to differentiate between healthy and heart failure patients (Example 6 and claims 28-39).

In summary, Karl et al. teach that like BNP, NT-proBNP is also a diagnostic marker in heart failure, but that NT-proBNP is more stable than BNP. When taken together with the teachings of MacDonald et al. (in which BNP was assessed in the context of canine heart failure), it would have been obvious to one of ordinary skill in the art to detect canine NT-proBNP instead of canine BNP in the method of MacDonald et al. One would be motivated to do this because Karl et al. taught that the former was known to be a more stable biomarker; as such, assessing changes in the levels of NT-proBNP in the disease state would be less subject to biomarker degradation which would be expected to adversely affect measurements. In addition, patient samples could be stored for longer periods of time before being assayed.

In carrying out assays for canine NT-proBNP, it would have been further obvious to follow the immunoassay strategy set forth in Karl et al., which directs the skilled artisan to employ two antibodies specific for the amino-terminal fragment of pro-BNP or NT-proBNP.

As discussed above, Karl et al. suggests antibodies that recognize amino acids 10-66, 10-50, or 10-38 of the 76-residue human NT-proBNP molecule; and exemplifies antibodies that recognize amino acids 30-38.

Liu et al. teach that the nucleotide and amino acid sequences of BNP have been identified for several mammalian species, including human and dog (page 188, right column). Liu et al. teach that sequence similarity of BNP genes provides strong evidence of related function in mammalian species abstract and page 188, right column, first full paragraph). In Figure 3, the full-length sequences of preproBNP from dog, human, and other species are aligned to show similarities among species:



In their publication, Liu et al. reported the newly identified cat BNP sequence and discuss how this information now allows for antibodies to be generated using synthesized antigenic

peptides for immunological assay development, and in particular for clinical applications (paragraph bridging pages 188-189).

This indicates that with knowledge of a protein's amino acid sequence, antibodies can be produced against the protein in order to detect the protein by clinical immunoassay. While the cat BNP sequence was newly reported by Liu et al., the sequence for canine preproBNP was previously known in the art (Liu et al., page 183, right column; and Figure 3). Liu et al. also teach that antibodies to BNP were known in the art to be species-specific (page 183, last column).

It is noted that the above sequences of Liu et al. are for preproBNP, and include the N-terminal signal peptide, which 26 amino acids in length in the case of the feline, canine, and human sequences (see Liu et al., abstract).

Based on the detailed sequence information known in the prior art about the human and canine proBNP molecules (as taught by Liu et al.), one of ordinary skill in the art would have found it obvious to design and raise antibodies against canine NT-proBNP. For example, it would have been obvious to produce canine NT-proBNP in recombinant form as was done by Karl et al. for human BNP, and to raise antibodies against this molecule.

In particular, based on the teachings of Karl et al. that antibodies against residues 30-38 human proBNP can successfully be used to detect human NT-proBNP in clinical assays, one of ordinary skill in the art would have found it obvious to raise antibodies that bind within the corresponding regions of canine NT-proBNP.

Although the canine and human proBNP sequences do not align exactly, differing in length, the teachings of Liu et al. provide detailed information about how the amino acids in the sequence of human proBNP correspond to those in canine proBNP.

Examining the sequence alignment of Liu et al. above, it can be readily seen that amino acids 30-38 of human proBNP (ELQVEQTSL; SEQ ID NO:8 in Karl et al.) correspond to amino acids 37-45 of canine proBNP (subtracting the 26-amino acid N-terminal signal sequence):

30-38 (human): ELQVEQTSL

37-45 (canine): ELQAEQLAL

This canine amino acid sequence lies entirely within the sequence depicted as amino acids 32-48 in the instant specification (Figure 1B).

Therefore, when producing antibodies against the canine sequence analogous to amino acids 30-38 of human proBNP, it would necessarily follow that the resulting antibodies would be specific for an epitope within amino acids 32-48 of canine proBNP.

In addition, based on the findings of Karl et al. that amino acids 30-38 of human proBNP (ELQVEQTSL) was one of two epitopes which showed the strongest reaction with the polyclonal antibodies they elicited [0084], as well as the strong sequence similarity between human and canine proBNP taught by Liu et al., it would also be reasonably expected that polyclonal antibodies raised against canine NT-proBNP would also be reactive with the epitope corresponding to amino acids 30-38 of human NT-proBNP.

For all of these reasons, in light of the known work in the human proBNP field by Karl et al., and together with the detailed sequence information available in the art (as taught by Liu et

al.), the Examiner finds that the differences between the claimed invention and the prior art were encompassed in known variations.

With respect to claim 32, Karl et al. teach that usually an epitope is clearly defined by 6 to 8 amino acids [0016]. In light of this evidence, it is presumed that the antibodies raised against canine NT-proBNP would possess the recited characteristics.

With respect to claims 33 and 58, Karl et al. teach that the antibodies may be either monoclonal or polyclonal [0025].

With respect to claims 34-36, Karl et al. teach that the antibody may be labeled for example with the hapten digoxigenin, which is then again bound by a further digoxigenin-specific antibody so as to allow for detection [0030]. This further antibody is itself labeled, for example with an enzyme such as peroxidase. Therefore, it would have been further obvious to employ such a further antibody in this manner so as to allow for detection of the results of the assay of MacDonald et al. and Karl et al.

With respect to claim 37, the immunoassay of Karl et al. involves binding one of the two antibodies to a solid phase [0026].

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re*

Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 29, 31-38, 47, and 57-58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 12/394,731. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application also claims a method of detecting canine proBNP or a fragment thereof in a canine sample by contacting the sample with at least one antibody that binds to an epitope within the region from amino acids 32 to 48 of canine proBNP (see especially claims 1 and 7). The epitope may comprise at least 3 amino acids (see claims 2 and 14) and may be either monoclonal or polyclonal (claims 3-4). Detection may be via radioimmunoassay, immune binding assay, Western blot, immunohistochemistry, or enzyme immunoassay (see claim 6) and may employ peroxidase, biotin, fluorescent dye, gold colloid, or a radionuclide as labels for the antibody (see claim 16).

With respect to claim 47, although copending Application No. 12/394,731 fails to specifically recite a step of obtaining the antibody, it would have been obvious to do so as a necessary step before the antibody could be used in the recited method.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

19. Applicant's arguments filed 7/14/09 have been fully considered but they are not persuasive.

20. With respect to issues of Sequence Compliance, as correctly pointed out by Applicant an electronic sequence listing has been filed for this case. The Notice to Comply attached to the prior Office action was in error and is hereby withdrawn.

21. Regarding the objection to the specification on the basis that the title of the invention is not descriptive, no amendments to the title have been made and Applicant's Reply does not include arguments pertaining to the objection, which is therefore maintained for reasons of record.

22. With respect to incorporation by reference issues, Applicant argues that the recitation of a full-length proBNP sequence in the specification is not essential (Reply, pages 8-9). Such remarks are not on point because the Office has not required a recitation of the full-length sequence.

At issue is that the claims recite "**amino acids 20 to 86 of canine proBNP**".

The examiner has made mention of the fact that the full amino acid sequence of canine proBNP is also not disclosed in the specification because if this were the case, the meaning of "**amino acids 20 to 86 of canine proBNP**" could be ascertained by reference to the full-length sequence.

However, in the instant case neither the sequence "**amino acids 20 to 86 of canine proBNP**" is not depicted in the Figures or disclosed elsewhere in the specification; nor is the full-length sequence disclosed by which one might ascertain the intended sequence. As such, the

specification does not identify what sequence corresponds to "**amino acids 20 to 86 of canine proBNP**" or otherwise provide a basis for understanding the scope of this term.

Applicant further argues that there is no *per se* requirement that an invention that involves a biomolecule must contain a recitation of the molecule's known structure in order to adequately describe the invention, pointing to the case of Falkner v. Inglis (Reply, pages 8-9). This is not found persuasive because in this case, the need for sequence information regarding "**amino acids 20 to 86 of canine proBNP**" does not arise out of a *per se* requirement but rather out of a need to clarify the meaning of this term.

Applicant further argues that a patent need not teach what is well known in the art; and that in this case, the amino acid sequence of canine proBNP is available from a publicly accessible source identified in the specification (Reply, page 9).

This is not found persuasive for reasons of record. Applicant apparently acknowledges that information from a public database is essential in order to determine what sequence is intended by "amino acids 20 to 86 of canine proBNP". **However, such subject matter has not been effectively incorporated by reference.**

Furthermore, while Applicant points to the database sequence recited in P16859 as being the sequence of proBNP, as noted in the prior Office action, there are discrepancies between this sequence and those sequences disclosed in the instant specification.

In view of these issues, it is maintained that the specification does not provide enough information to adequately identify the recited amino acid sequences.

23. With respect to the rejections under § 112, 1st paragraph, points (1) and (2), Applicant argues that the claimed methods do not require one to distinguish between full-length proBNP and fragments thereof, and points to the instant amendments to recite determination of "proBNP and fragments thereof" (Reply, page 9).

To clarify, this aspect of the rejection was made on the basis of the language in the conclusion step, in that "determining the presence and/or concentration of…canine proBNP, or fragments thereof, present in the sample" could be read as meaning that each of these species may be separately determined (since the species were recited in the claim separated by commas).

It appears that Applicant is in agreement that the claimed methods would not distinguish between proBNP and fragments thereof. Rather, a positive signal would indicate that either proBNP or fragments thereof comprising the antibody epitope were present. However, the amendments to now recite that the method determines "proBNP and fragments thereof" still implies that the method can determine whether proBNP is present AND whether fragments thereof are present.

To obviate this aspect of the rejection, it is suggested that the claims recite a method of "determining canine proBNP or fragments thereof" in the preamble and conclude with the step of "determining the presence and/or concentration of canine proBNP or fragments thereof".

With respect to point (3), no arguments addressing this aspect of the rejection could be found as part of Applicant's Reply.

With respect to point (4), Applicant argues that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied. Applicant further

argues that failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under § 112, 1st paragraph. Applicant further argues that the examiner's interpretation of the claim as encompassing bispecific antibodies is improperly requiring enablement of a limitation that is not recited in the claim. See Reply, pages 9-10.

Applicant's remarks are found persuasive and accordingly, this aspect of the rejection has been withdrawn.

24. With respect to the rejections under § 112, 2nd paragraph, Applicant argues that one of ordinary skill in the art would be able to identify amino acids 20 to 86 of canine proBNP by using the information in Figure 1B of the specification together with the database sequence published as Swiss-Prot Accession No. P16859 (Reply, page 11).

This is not found persuasive because it appears that Applicant acknowledges that reference to the database sequence information would be necessary in order to determine what is meant by the claim term "amino acids 20 to 86 of canine proBNP". However, such database information has not been effectively incorporated by reference (see above).

Furthermore, in the instant case the database sequence information cannot be clearly correlated with the claimed sequence. In this regard, Applicant argues that if the first 26 amino acids of P16859 are disregarded, it would be the same numbering scheme used in the instant specification (Reply, page 11). This is not found persuasive because there is nothing in the instant specification that directs the skilled artisan to disregard the first 26 amino acids.

For all of these reasons, it is maintained that it is not possible to uniquely identify what amino acid sequence is meant by "amino acids 20 to 86 of canine proBNP".

25. With respect to the rejections of claims 29, 31-33, 37-38, 47, and 57-58 under 35 U.S.C. 103(a) as being unpatentable over MacDonald et al. in view of Asada et al. and in light of the evidence of Harlow & Lane, the Academic Press Dictionary of Science and Technology, Janeway et al., and Wolfe; and of claims 34-36 as being unpatentable over these references and further in view of Harlow & Land 2; Applicant's arguments (Reply, pages 12-14) have been fully considered but are not found persuasive.

Applicant argues for unpredictable factors, in that it was not previously known which fragments of canine proBNP circulated in blood or whether the amount of any such fragments was sufficient to be detected by immunoassay. Applicant argues that Asada discloses that *human* BNP exists primarily in blood as proBNP rather than BNP-32, but that Asada does not disclose which form of *canine* BNP is predominant. See Reply, page 12.

This is not found persuasive because Asada clearly contemplates any mammalian proBNP and also specifically mentions canine proBNP (see [0010] and claim 1). The statements made by Asada that in blood, BNP exists in the form of proBNP or its degradation product, and not in the form of BNP-32 which was previously considered dominant [0008], are made generally and are not qualified as referring only to human BNP as apparently perceived by Applicant.

For these reasons, Applicant's arguments do not constitute sufficient evidence of unpredictability. In particular, no extrinsic evidence is apparent that those of skill in the art would doubt that proBNP is present in canine blood in sufficient levels for immunoassay. There is no evidence presented, for example, that others tried and failed to find proBNP in dogs.

Rather, reading Asada one of ordinary skill in the art would understand the disclosed methods of proBNP assay to be applicable to any mammalian species, including canine.

Applicant further argues that MacDonald et al. present data to show that human BNP concentrations increase with age, while dog BNP concentrations do not (Reply, page 13). Applicant argues that therefore, not all observations regarding human BNP apply to canine BNP. Applicant further argues that the sequences of canine and human proBNP show considerable variation, and that there is little cross-reactivity between antibodies produced against epitopes of each species. Applicant speculates that these structural differences could result in different half-lives and/or different fragmentation patterns, but does not provide evidence of this. Applicant also points to the Liu reference as evidence of unpredictability in making inter-species predictions about proBNP. Applicant concludes that it would have been unpredictable whether one could have successfully modified the method of MacDonald based on the teachings of Asada in order to arrive at the claimed method.

This is not found persuasive because in the instant case, the evidence of MacDonald et al. establishes a nexus between cardiac disease in dogs and BNP. As such, whether there is also nexus between age and BNP in dogs is not seen as material, as this is not the subject of Applicant's claimed invention.

Furthermore, the teachings of Asada indicate that those of skill in the art recognized that either BNP or its precursor, proBNP, could be assayed in the context of heart disease in mammals; but that the latter is more stable. As such, the observation that the sequences of canine and human proBNP may differ does not in itself constitute evidence of unpredictability. Likewise, the fact that antibodies raised against one species do not cross-react with another

species does not necessarily mean that the proteins differ in function (see also the discussion of Liu et al. below).

It may be that for some proteins, homologs in different species could give rise to significant functional differences. However, there is no evidence that this is the case here; rather, the knowledge in the art regarding BNP and proBNP in mammals was such that a correlation with disease was well-recognized.

In summary, Applicant's arguments are not found to constitute sufficient evidence of unpredictability. It is therefore maintained for reasons of record that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention based on the teachings of Asada et al. and MacDonald et al.

26. With respect to the rejections of claims 29, 31-38, 47, and 57-58 under 35 U.S.C. 103(a) as being unpatentable over MacDonald et al. in view of Karl et al. and Liu et al., Applicant's arguments (Reply, pages 14-16) have been fully considered but are not found persuasive..

Applicant argues as above that MacDonald et al. present data to show that human BNP concentrations increase with age, while dog BNP concentrations do not (Reply, page 15). Applicant argues that therefore, not all observations regarding human BNP apply to canine BNP. Applicant further argues that the sequences of canine and human proBNP show considerable variation, and that there is little cross-reactivity between antibodies produced against epitopes of each species. Applicant speculates that these structural differences could result in different half-lives and/or different fragmentation patterns, but does not provide evidence of this. Applicant also points to the Liu reference as evidence of unpredictability in making inter-species

predictions about proBNP, in that the reference documents differences in sequences between species and teaches that "antibodies of BNP are species specific". Applicant concludes that it would have been unpredictable whether one could have successfully modified the method of MacDonald based on the teachings of Asada in order to arrive at the claimed method.

This is not found persuasive because as discussed above, while it may be the case that some proteins differ significantly in function across species, there is no evidence that this is the situation here. The fact that the sequences between canine and human proBNP exhibit variability is to be expected as a result of the species difference. Likewise, the fact that antibodies do not cross-react is an expected corollary of such sequence differences.

Nonetheless, in the instant case there is insufficient evidence that one of ordinary skill in the art would have expected significant functional differences to arise due to this expected inter-species variability.

Rather, while Applicant focuses on the variation among the sequences, the evidence of record indicates that despite such variation the knowledge in the art regarding BNP and proBNP was such that a correlation was recognized with heart disease for mammals in general. This is indicated not only by the teachings of Asada et al. as discussed above, by also by Liu et al., who state in the abstract that:

> Brain (B-type) natriuretic peptide (BNP) is a cardiac hormone involved in regulation of fluid balance and blood pressure homeostasis of mammalian species. BNP sequence is species-specific and considered to be a significant prognostic and diagnostic marker for cardiac dysfunction.

Therefore, despite the fact that inter-species sequence differences were known in the prior art, a common function for BNP-related molecules was appreciated. For all of these

reasons, there is insufficient evidence to adopt Applicant's position that one of ordinary skill in the art would lack a reasonable expectation of success.

27. Regarding the provisional double patenting rejection over copending Application No. 12/394,731, Applicant acknowledges but does not presently address the rejection (Reply, page 16), which is therefore maintained at this time for reasons of record.

Conclusion

28. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571)

272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641

/Christopher L. Chin/
Primary Examiner, Art Unit 1641